



Formulation and Evaluation of Celecoxib Solid Dispersion

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Abstract

Aim: The purpose of present study is to develop stomach specific celecoxib solid dispersion using eudragit EPO as a carrier for enhancing solubility as well as rate in gastric environment.

Method: Enhanced dissolution rate and solubility in gastric pH was achieved by formulating celecoxib solid dispersion by hot melt extrusion techniques. The celecoxib solid dispersion prepared by 2² factorial design. The drug and eudragit EPO in different ratios like 1:1, 1:2, 1:3 and 1:4 were used for formulating solid dispersion. **Results:** FTIR spectra of celecoxib in alone and combination showed compatibility of drug and excipient. The solid dispersion was evaluated for percentage yield, drug content and percent drug release and results found to be 97.50%, 99.43% and 87.97% respectively. Stability study was performed in closed container at 30 °C ± 2 °C/65% RH ± 5% RH and 40 °C ± 2 °C/75% RH ± 5% RH. **Conclusion:** It was concluded that 1:1 ratio of celecoxib solid dispersion shows better in-vitro dissolution rate as compared to pure drug. The increased dissolution rate of celecoxib solid dispersion in gastric pH was attributed to the effect of eudragit EPO which was clearly shown by SEM, DSC and P-XRD studies.

Keywords

Celecoxib, Eudragit EPO, Solid dispersion, Hot melt extrusion.

INTRODUCTION

Celecoxib is 4-[5-(4-methyl phenyl)-3-(trifluoromethyl)pyrazole-1-yl]benzyl sulphonamide (IUPAC). The chemical formula of celecoxib is C₁₇H₁₄F₃N₃O₂S and molecular weight is 381.373 g/mol. (3) The celecoxib is poorly water soluble drug belonging to the class of selective cyclooxygenase-2 (COX-2) inhibitors. It is clinically used in treatment of osteoarthritis, acute pain, ankylosing spondylitis and rheumatoid arthritis. Celecoxib belonging to the biopharmaceutics classification system (BCS) class second because of its low solubility and high permeability. (8) Being categorized class second compound as per biopharmaceutics classification system; celecoxib

possesses very poor bioavailability. Moreover it is important to improve solubility as well as bioavailability of celecoxib. There are several ways to enhance bioavailability of drug which aimed at increasing the surface area of drug which includes solvent disposition, solvent complexation, solid dispersion, solute solvent complexation. The most favourable method for promoting dissolution is formation of solid dispersion. The term solid dispersion is defined as dispersion of one or more active ingredient in an inert carrier or matrix in solid state prepared by melting solvent or hot melt extrusion method. (13) Hot melt extrusion (HME) has proven to be a robust method for producing solid dispersion which increases the bioavailability of

drug. The hot melt extrusion is the process of pumping raw material at elevated controlled pressure and temperature through a heated barrel of melt extruder into a product of uniform shape and density. In short extruder is composed of feeding hopper, barrels, twin screws and screw driving unit. (19) The methacrylate polymer with the brand name eudragit EPO has been used in preparation of solid dispersion. Eudragit EPO dissolves in gastric pH because of its basic characteristic containing tertiary amino group which are ionized in gastric pH. In the present study eudragit EPO as polymer for preparation of celecoxib solid dispersion; which has property of an immediate drug release in gastric pH condition. The formulation with different drug polymer ratios 1:1, 1:2, 1:3 and 1:4 were prepared and solid dispersion was obtained by hot melt extrusion technique. In the dissolution study of solid dispersion 1:1 ratio showed highest dissolution rate. Differential scanning calorimetry (DSC), powder X-ray diffraction (P-XRD), scanning electron microscopy (SEM) were performed for physical characterization of Celecoxib solid dispersion. Formulation of Celecoxib solid dispersion was optimized by 2² factorial design. (20)

EXPERIMENTAL:

Material

Celecoxib gift sample obtained from Sigma Laboratories Pvt. Ltd, Mumbai. Eudragit EPO obtained from S.D. Fine Chem Ltd, Mumbai. All chemicals used in the formulation preparation were of analytical grade and used without further purification.

Characterization study of drug

The sample of drug observed for colour and state. (12) The melting point of celecoxib determined by taking amount of drug in a capillary which is closed at one end and placed in the thials tube containing liquid paraffin by continuous heating at the bottom of the thiles tube. The melting point was noted with the help of thermometer. The UV spectrum of celecoxib was obtained using UV visible

spectrophotometer (JASCO-V-530). The FTIR spectra of celecoxib and physical mixture was obtained using KBr pellet method. The thermal characteristic of celecoxib and physical mixture studied using SHIMADZU DSC TA60 VVS thermal analyzer.

Analytical method development

The calibration curve of celecoxib in water and methanol was prepared by plotting absorbance vs concentration of celecoxib. The first stock solution was prepared by accurately weighing 10 mg of drug in 10 ml of methanol and volume made with 10 ml. After that 1 ml stock solution taken from stock 1st and dilute upto 10 ml. Different aliquots were taken from stock 2nd and diluted with distilled water to prepare series from 5-25 µg/ml. Absorbance was measured at λ_{max} against distilled water as a blank by UV visible spectrophotometer (JASCO-V-530). (14,10)

IR spectroscopy

In the preformulation studies it is very important to check the drug is not interacting with polymer. It should be compatible with the polymer under certain experimental studies. Interaction between drug and polymer affect the efficacy of final dosage form. The drug and polymer were taken in 1:1 ratio. The studies performed from Seth Govind Raghunath College of Pharmacy, Saswad, Pune.

Method of preparation of solid dispersion: -

The solid dispersion of celecoxib prepared by hot melt extrusion method by a twin screw extruder (Eurolab 16). Firstly, switched on the electrical mains of the hot melt extruder and pressed the reset button to set the program. The blend of celecoxib and eudragit EPO in different ratios loaded in feeder hopper. Then started the extruder and feeder; increases the screw rpm and started the vacuum pump. During the operation monitored torque, pressure and melt temperature. Then collected the extrudates in container. Four different formulations of Celecoxib solid dispersion prepared with eudragit EPO polymer in four different ratios 1:1, 1:2, 1:3 and 1:4.

Table 1: Formulation composition of solid dispersion

Sr.No.	Formulation code	Drug (mg)	Polymer (mg)
1	F1	100	100
2	F2	100	200
3	F3	100	300
4	F4	100	400

Evaluation of celecoxib solid dispersion: - Aqueous solubility study

The solubility studies were performed on pure drug and solid dispersion. This test conducted in orbital shaker for 24 hours at 37 °C ± 5 °C. Finally, the solution

were filtered using whatman filter paper and filtrate was diluted to 10µg/ml for determining drug concentration by UV visible spectrophotometer. The absorbance was measured at 253nm.

Drug content

The accurately weighted quantity of solid dispersion equivalent to 100 mg of celecoxib taken into 100 ml volumetric flask and dissolved in acetonitrile. This solution filtered by whatman filter paper. Then 5ml of filtrate diluted to 100ml with 1% SLS solution and assayed for drug content using UV visible spectrophotometer at 253nm. All dispersion contained 100±5% of drug. (13,24)

Percentage yield

The well dried solid dispersion was collected and weighed accurately. The percentage yield was calculated by using formula given below.

%yield = Mass of SD obtained / Total weight of drug + polymer x 100. (12,19)

In-vitro drug release study

The in vitro study of pure drug and its solid dispersion carried out using USP apparatus 2nd (LABINDIA DS 8000). The dissolution medium was 900ml 0.1 N HCL (pH 1.2) kept at 37±1°C. The paddle was rotated at 100 rpm. The sample of 5ml were withdrawn at specified time interval and analysed spectrophotometrically at 253nm using UV visible spectrophotometer. The sample withdrawn replaced by fresh 0.1 N HCL solution. The dissolution study continued for next 2 hr. (12,21)

Micromeritic studies

Bulk density(ρ_b) = Mass of powder(M) / volume of bulk powder (V_b) x 100

Tapped density(ρ_t) = total mass of powder(M) / tapped volume of powder (V_t) x 100

Carr's index = (Tap density – bulk density / Tap density) x 100

Hausener's ratio = Tapped density(ρ_t) / Bulk density(ρ_b)

Angle of repose (θ) = $\tan^{-1} (h/r)$

Where, h= height, r= radius

FTIR spectroscopy study

The FTIR spectra of solid dispersion 1:1 ratio was recorded SHIMADZU FTIR spectrophotometer. The sample scanned at 4000 – 400 cm^{-1} . (14)

Differential scanning calorimetry

DSC pattern of solid dispersion in 1:1 ratio was recorded using METTLER TOLEDO. (15,7)

P-X ray diffraction

Powdered X-ray diffraction of pure and solid dispersion in 1:1 ratio recorded on D8 Advanced diffractometer. (14,23)

RESULT AND DISCUSSION

Preformulation studies of drug

The properties of drug related with the physical appearance, state solubility are given below table no.2

Table 2: Description of drug

Sr.No	Properties	Nature
1	State	Crystalline
2	Colour	White
3	Solubility	Poorly soluble in water, soluble in methanol, DMSO, chloroform, acetonitrile etc.

The melting point of Celecoxib was found to be 160°C.

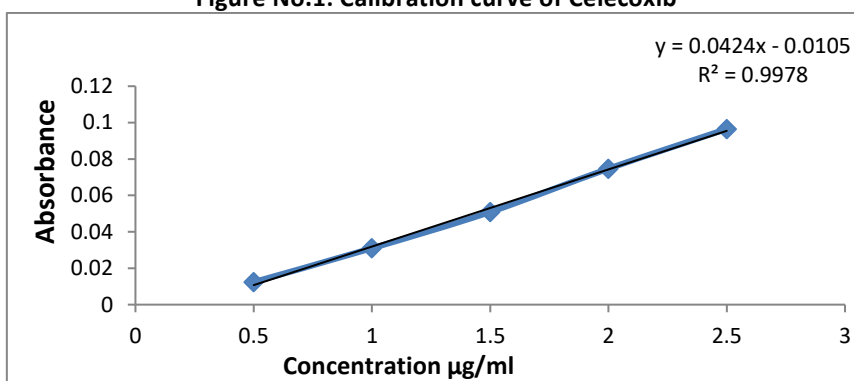
Analytical method for celecoxib using std. calibration curve

Analytical method was developed for analysis of Celecoxib in powder in chloroform using UV visible spectroscopy. The method obeyed beer's law and found suitable for study. The std. calibration curve of Celecoxib in chloroform is shown in figure no.1.

Table 3: UV absorbance of Celecoxib

Sr.No	Concentration(µg/ml)	Absorbance
1	5	0.0124
2	10	0.0310
3	15	0.0509
4	20	0.0741
5	25	0.0965

Figure No.1: Calibration curve of Celecoxib



Drug excipient compatibility study

The interaction between drug and physical mixture were studied by IR spectroscopy. Below spectra shows the peak of pure drug and physical mixture that is i.e no chemical reaction occurs between

polymer and drug sample as shown in figure no.2 and 3. FTIR spectra studies showed the following characteristic peak at 1219 cm^{-1} due to C-F stretch, 2916 cm^{-1} due to C-H₃ stretch, 1481 cm^{-1} due to C=C aromatic group, 3487 cm^{-1} due to N-H stretch.

Figure No.2: FTIR spectra of pure Celecoxib

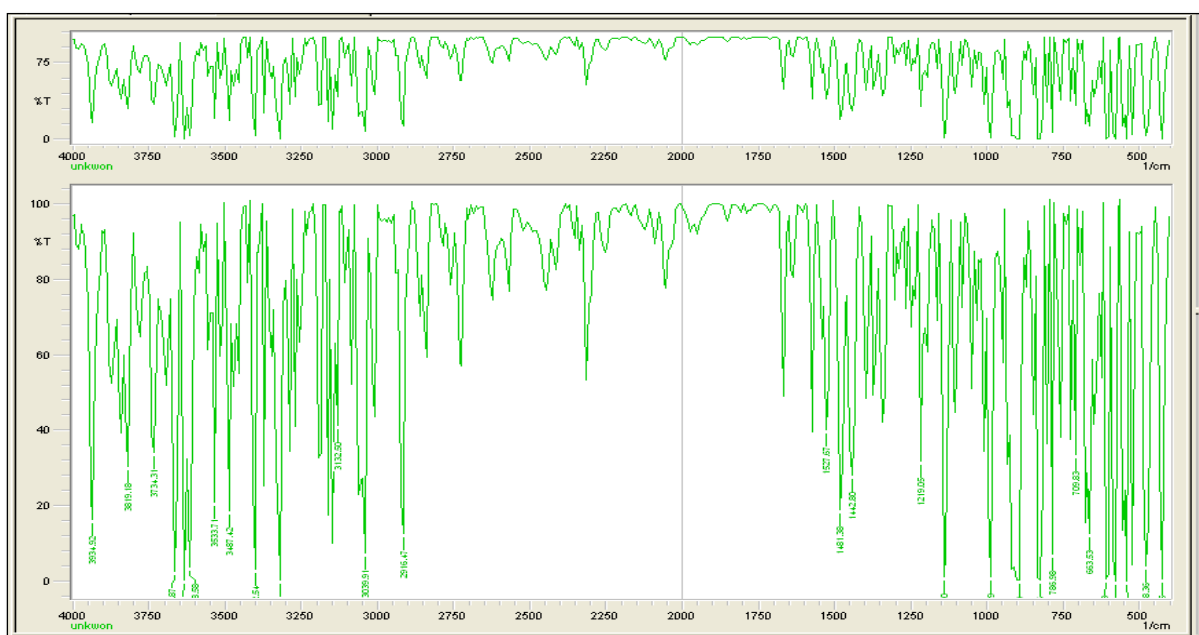
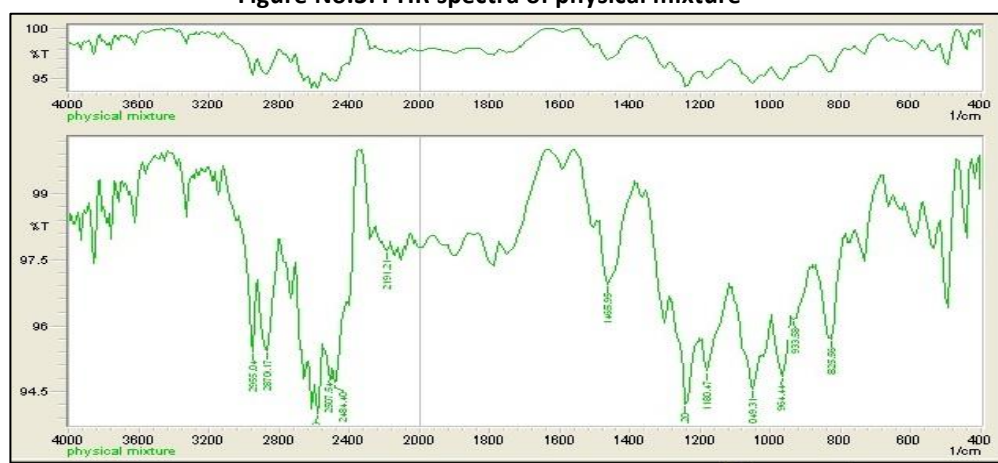


Figure No.3: FTIR spectra of physical mixture



peak obtained in the spectrum of pure drug were similar to that given in std.

Differential scanning calorimetry

The DSC thermogram of Celecoxib and physical mixture was recorded and it shows one endothermic

peak at 163 °C. This was compared and accordance with reported DSC data of drug. Celecoxib was identified by DSC as shown in figure no.4 and 5.

Figure No.4: DSC thermogram of Celecoxib.

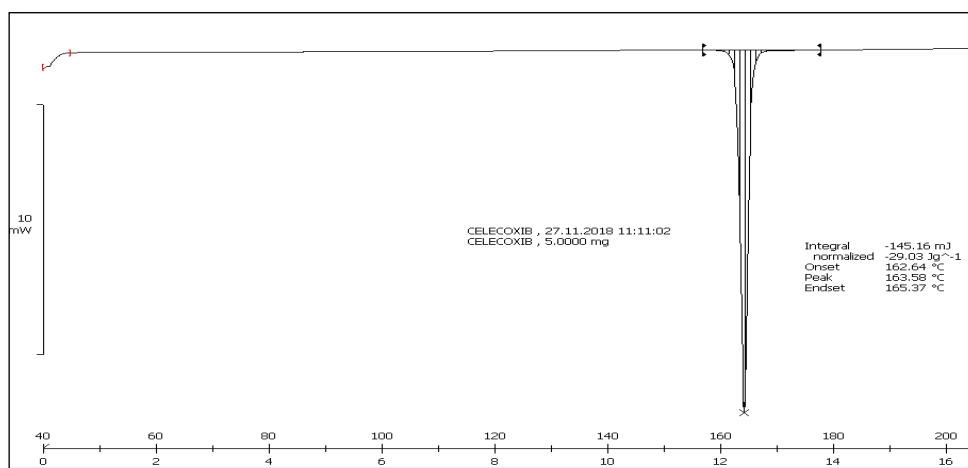
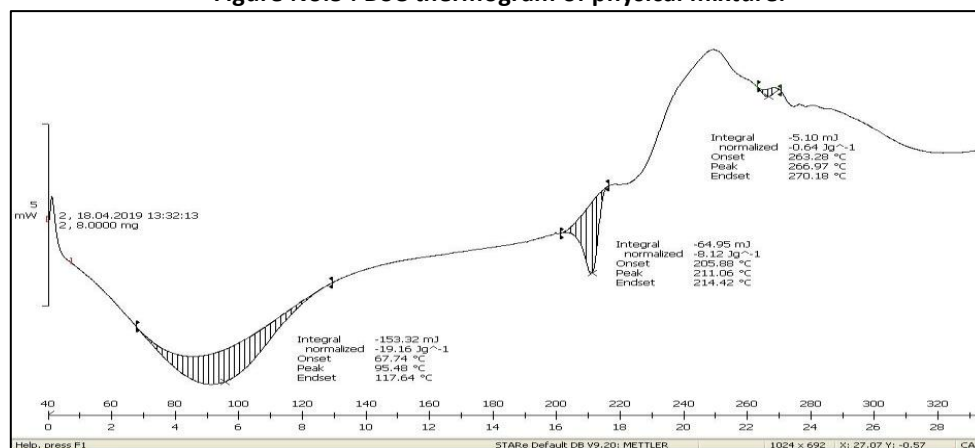


Figure No.5 : DSC thermogram of physical mixture.



From the above data on the basis of physical appearance, melting point, UV visible spectrum, FTIR spectrum and DSC thermogram of celecoxib. The procured sample of celecoxib was found to be acceptable purity and quality. The sample taken for further studies.

Evaluation tests: -

The solubility of celecoxib and solid dispersion was determined in triplicate and average values were reported in table no.4.

Table 4: Solubility of Celecoxib solid dispersion.

Sr.No.	Formulation code	Solubility in 0.1 N HCL
1	API	3.447±0.16
2	F1	53.92±0.48
3	F2	11.55±0.21
4	F3	14.22±0.42
5	F4	25.31±0.45

From the solubility readings it was found that solid dispersion prepared using eudragit EPO in 1:1 ratio had good solubility as compared to other drug polymer ratio. For the further study 1:1 ratio of solid dispersion selected and evaluated.

Micromeritic studies

In these studies the flow properties of pure drug and solid dispersion studied and the obtained results are as shown in table no.5

Table 5: Micromeritic properties of Celecoxib solid dispersion

Sample	Bulk density	Tapped density	Housner's ratio	Carr's index	Angle of repose
Pure drug	0.358	0.550	1.53	34.90	42°.35
F1	0.501	0.536	1.06	6.52	22°.11
F2	0.482	0.538	1.11	10.40	25°.13
F3	0.470	0.539	1.14	12.80	27°.22
F4	0.495	0.537	1.08	7.82	24°.14

Percentage yield

The percentage yield of prepared solid dispersion is determined and shown in table no.6

Table 6: Percentage yield of solid dispersion

Sr.No.	Formulation batch	Percentage yield
1	F1	97.50%
2	F2	96.33%
3	F3	95.25%
4	F4	96.80%

Drug content

The drug content of different solid dispersion is shown in table no.7

Table 7: Drug content of solid dispersion.

Sr.No.	Formulation batch	Drug content
1	F1	99.43%
2	F2	98.51%
3	F3	102.30%
4	F4	101.50%

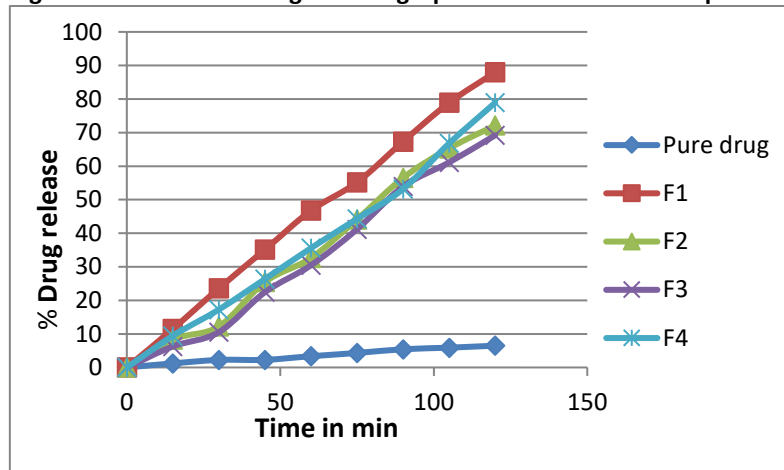
In-vitro drug release study

The dissolution studies of pure drug and formulation were performed. Celecoxib solid dispersion showed better dissolution performance over corresponding

to pure drug. Celecoxib with Eudragit EPO solid dispersion (1:1) ratio showed a significant increase in cumulative % drug release upto 87.97% and shown in table no.8

Table 8 : In-vitro drug release study of solid dispersion with pure drug.

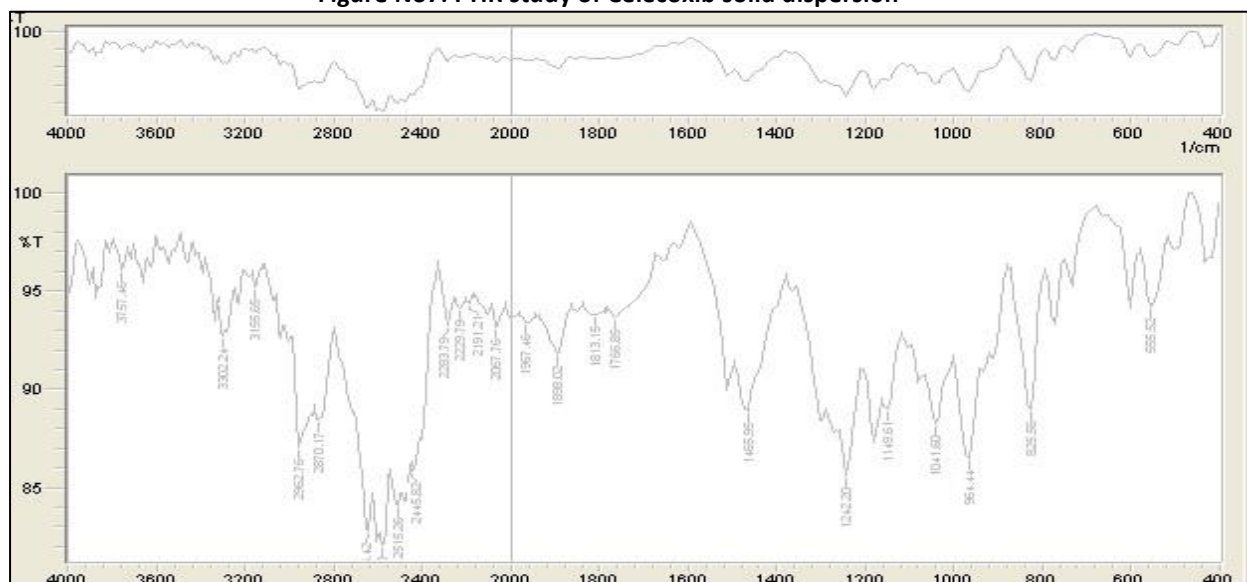
Sr.No.	Time (min)	0	15	30	45	60	75	90	105	120
1	Pure drug	0	1.22	2.24	2.28	3.35	4.32	5.43	5.90	6.50
2	F1	0	11.48	23.59	35.11	46.78	55.16	67.32	78.89	87.97
3	F2	0	8.34	12.24	25.49	32.63	44.13	56.51	65.29	72.14
4	F3	0	6.28	10.53	22.45	30.47	41.20	53.91	61.11	69.19
5	F4	0	9.44	17.26	26.36	35.58	44.29	53.18	66.78	78.90

Figure No.6 : In-vitro drug release graph of Celecoxib solid dispersion.


As per the percentage yield, drug content and dissolution studies result it indicated that F1 formulation batch gives better yield, having best drug content and shows best dissolution release.

FTIR spectroscopy

The FTIR spectra of Celecoxib and Eudragit EPO solid dispersion (1:1) ratio was recorded with FTIR spectrophotometer and shown in figure no.7

Figure No7: FTIR study of Celecoxib solid dispersion


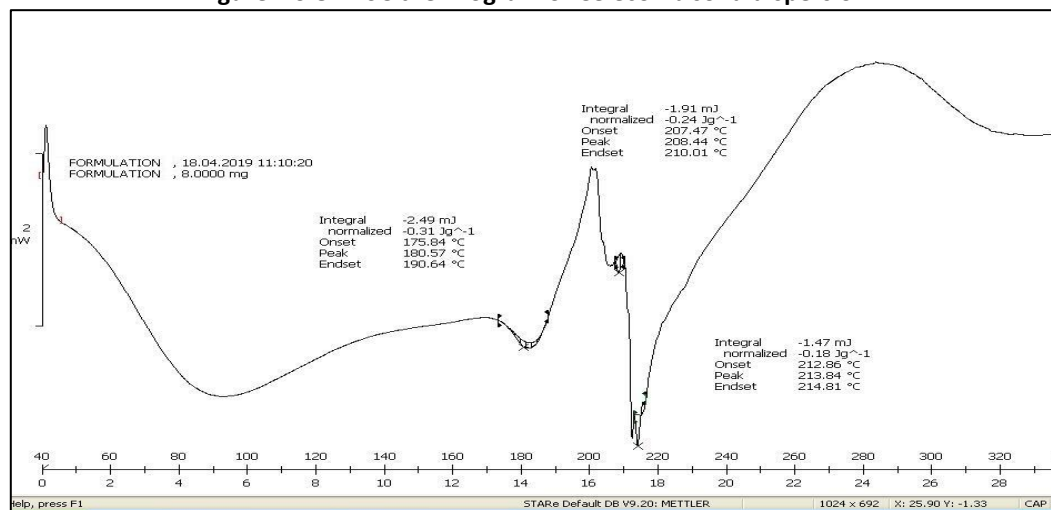
From the FTIR spectra of Celecoxib : Eudragit EPO solid dispersion (1:1) ratio was found that there is no

functional group change when Celecoxib react with Eudragit EPO. So they are found to be compatible with each other.

Differential scanning calorimetry

The DSC thermogram of Celecoxib : Eudragit EPO solid dispersion are shown in figure no.8

Figure No.8 : DSC thermogram of Celecoxib solid dispersion.



Powder X – ray diffractometry

X- ray diffractogram of Celecoxib and Eudragit EPO (1:1) ratio are shown in figure no.9 and 10.

Figure No.9 : X-ray diffractogram of Celecoxib.

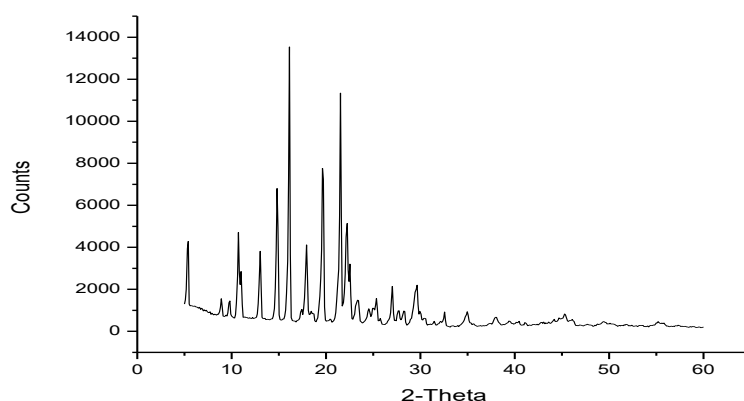
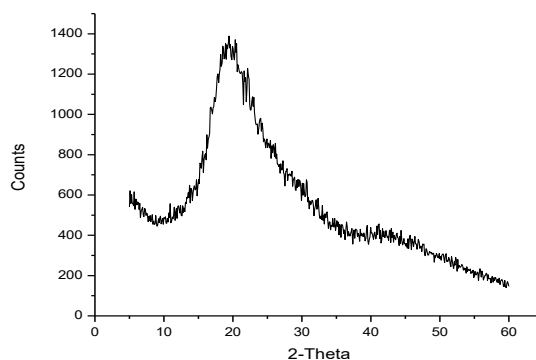


Figure No.10: X- ray diffractogram of Celecoxib solid dispersion.



The diffraction pattern of pure celecoxib showed its highly crystalline nature. The diffraction pattern of Celecoxib: Eudragit EPO solid dispersion shows the peak of Celecoxib with reduction in peak intensities indicating that conversion of crystalline to partial amorphous form.

Scanning electron microscopy

The particle size of pure drug and Celecoxib: Eudragit EPO solid dispersion determined by scanning electron microscopy studies and shown in figure no.11 and 12.

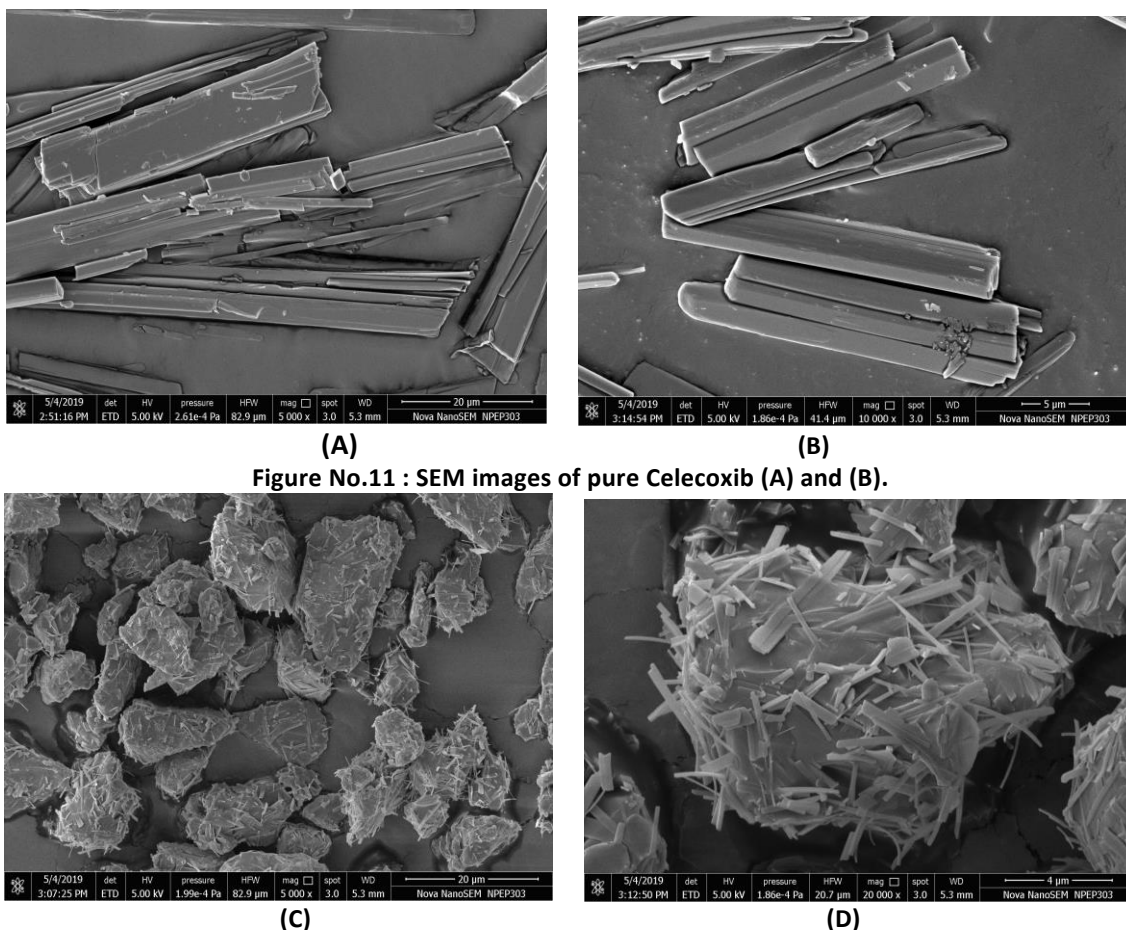


Figure No.11 : SEM images of pure Celecoxib (A) and (B).

Figure No.12 : SEM images of Celecoxib solid dispersion (C) and (D).

The SEM micrographs of celecoxib powder showed irregular shaped crystalline particles. On the other hand, formulation F1 was spherical in shape and smooth morphology and particle size 5µm.

Stability study

The stability study was performed on the optimized batch F1. Solid dispersion was kept in closed container at $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\% \text{RH}$ and $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\% \text{RH}$ for 3 months. The effect of storage was studied on the colour and drug content of the optimized batch at regular time intervals. There was no significant effect of presence/absence of light on observed at specific storage conditions. Based on results obtained on stability study of formulation F1; it can be concluded that the formulation is stable at $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\% \text{RH}$

and $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\% \text{RH}$ in both light and dark condition.

CONCLUSION

Celecoxib is BCS class second poorly water soluble drug having high permeability and low solubility. The aim of this study was to improve solubility as well as dissolution rate of Celecoxib. Therefore we prepared solid dispersion of Celecoxib with Eudragit EPO by using hot melt extrusion method. API used as control group. From the above studies it is concluded that the formulation with drug : polymer 1:1 showed better dissolution rate in comparison with API. The solid state characterization such that DSC, SEM, P-XRD studies gave information about smooth molecular morphology and strong molecular dispersion

between Celecoxib and Eudragit EPO solid dispersion exhibit an immediate release dissolution profile in 0.1 N HCL (pH 1.2) compared with pure celecoxib powder. Therefore developed formulation with immediate drug release profile could be an effective drug delivery system in treatment of osteoarthritis, rheumatoid arthritis, acute pain etc.

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REFERENCES

1. Yasmin M, Abbulu K, Sudhakar M, et.al. Celecoxib – encapsulated liposomes of long alkyl chain lipids: Formulation, characterization and *in vitro* performance. *Pelagia Reserch Library*. 2012 ; 3(1): 117-125.
2. Ahmed S, Samy E, Ahmed M, et.al. Formulation and In vitro evaluation of celecoxib buccoadhesive tablets. *Journal of American science*.2016; 12(8): 69-77.
3. Lee J, Lee D, Khang G, Enhanced dissolution rate of celecoxib using PVP and/or HPMC – based solid dispersion prepared by spray drying method. *Journal of pharmaceutical investigation*. 2013;6:205-2013.
4. Vikram P, Dhaval P, Jayvadan P, et.al. Formulation ,characterization and optimization of fast dissolve tablets containing celecoxib solid dispersion. *Dissolution technologies*. 2009;11:22-27.
5. Sankha B, Bhupenura P. Preparation and evaluation of celecoxib polysaccharide-based matrix tablets using nanoparticulate approach. *Asian journal of pharmaceuticals*. 2017;6 (5):374-381.
6. Nagabhashanam M. Formulation studies on solid dispersion of celecoxib in superdisintegrants alone and with PVP. *Rasayan J.chem*. 2019;3(2):691-698.
7. Swati R, Laila A, S K J, et.al. A comparative dissolution study of commercial and prepared formulation of celecoxib. *Indian journal of pharmaceutical science*.2005;10(9):632-634.
8. Eun –Sol Ha, Gwang –Ho Choo, In-Hwan Baek, et.al. Formulation characterization and in vitro evaluation of celecoxib PVP solid dispersion nanoparticles using supercritical antisolvent process. *Molecules*. 2014;11(4):20325-20339.
9. Sanjeev C, Ranendra S. Development and in vitro evaluation of oral controlled release formulation of celecoxib using optimization technique. *Researchgate*. 2016; 8:505-514.
10. Bharath D, Aruna C. Formulation of celecoxib into immediate release tablets. *An international journal of advances in pharmaceutical science*.2010;12(2):318-326.
11. Shahazad M, Ubaid M, Murtaza G, et.al. Formulation and optimization of celecoxib loaded microsphere using response surface methodology. *Tropical journal of pharmaceutical research*.2012;11(5):695-702.
12. Ankit G, Mahesh K, Ajay B, et.al. Formulation and evaluation of solid dispersion of glipizide for solubility and dissolution rate enhancement. *International journal of pharmaceuticals and drug analysis*. 2014;2(11):74-86.
13. Punitha S, Vedha N, Kartikeyan D, et.al. Enhancement of celecoxib solubility by solid dispersion using mannitol. *International journal of pharmacy and pharmaceutical science*. 2010;4(2):109-111.
14. Supriya W, Vilas A, Deepak D, et.al. Solubility enhancement of antiviral drug acyclovir by solid dispersion technique. *Indo american journal of pharmaceutical science*. 2015;2(10):1352-1365.
15. Roshan R, Sung K, Chul Y, et.al. Characterization of valsartan loaded eudragit EPO solid dispersion microparticles. *Asian journal of pharmaceutical science*. 2016;6(2):744-750.
16. Sharda S. Solid dispersion :A tool for improving the solubility and dissolution of metronidazole. *Researchgate*. 2015;8(19):94-98.
17. Manimaran V, Dhamodharan N, Mothilal M, et.al. Enhancement of dissolution rate of glibenclamide by solid dispersion technology. *International journal of current pharmaceutical research*. 2010;3(2):14-17.
18. Shrinivas Y, Vijaya L, Varalakshmi TSNS, et.al. Formulation and evaluation of carvedilol solid dispersion for dissolution rate enhancement. *Int. journal of advances in pharmacy, biology and chemistry*.2012;12(4):489-495.
19. Devendra R, Zsmond Z. Hot melt extrusion and its application for pharmacokinetic improvement of poorly water soluble drugs. *ResearchGate*.2016;2(3):47-51.
20. Shrinivasa K, Surya S, Prasad S, et.al. Optimization of valsartan SR floating tablet formulation by 2² factorial design and multiple regression technique. *Int.research journal of pharmacy and medical sciences*.2018;11(15):11-15.
21. Natalja G, Batol H, Karbinian L, et.al. Hot melt extrusion as solvent free technique for continuous manufacturing of drug loaded mesoporous silica. *Journal of pharmaceutical science*.2018:149-155.
22. Raviraj B, Manish S, Shivam S, et.al. Preparation and characterization of paloxamer based solid dispersion for effective enhancement of solubility of poorly water soluble drug. *Asian journal of pharmaceutical education and research*.2018;6:92-104.
23. Amrin S, Prashant B. Solubility enhancement of celecoxib by solid dispersion technique and incorporation into topical gel. *ResearchGate*. 2019; 1:294-300.



24. Sashmitha B, Swapna V, Amit B, et al. Preparation and evaluation of solid dispersion of celecoxib.

Int. journal of pharmaceutical sciences review and research. 2012; 17(1): 52-56.